IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Chopra, Sham	
Serial No. 10/697,473	Group Art Unit: 1614
Filed: October 30, 2003	Examiner: ANDERSON, JAMES D.
For: CHRONOTHERAPY TABLET AND METHODS RELATED THERETO	

DECLARATION OF Dr. Alain Desjardins UNDER RULE 1.132

I, Dr. Alain Desjardins, hereby declare that:

1. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, of both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

2. I am Vice President, Research & Development, Mistral Pharma Inc., Quebec, Canada. A full and accurate account of my qualifications including education, publications, titles, and awards, for example, is presented in my *curriculum vitae* (C.V.) as an appendix attached hereto.

3. I have intensively studied and developed controlled-release drug formulations for years in the pharmaceutical industry.

4. By training and experience I am familiar with the properties of pharmaceutical excipients and production processes employed in the formulation and conformation of tablets to achieve desired rates of drug release.

5. I am familiar with the statements in the present file of United States Application Serial No. 10/697,473, the specification, the claims, as well as the Amendment being filed with this Declaration.

6. I am not an inventor on the above-identified pending application.

7. I am familiar with the disclosure of Conte U.S. Patent 4,865,849.

8. Evidence presented in this declaration illustrate that drug release profiles achieved by tablets defined by the claims of the United States Application Serial No. 10/697,473 cannot be achieved by tablets disclosed and contemplated by Conte in U.S. Patent 4,865,849.

9. Particularly, data presented in Conte U.S. Patent 4,865,849 is compared to data produced from tablets prepared according to the procedure described in Patent Application 10/697,473 for the purpose of demonstrating that the drug release profiles presented by the former are vastly different from those achieved by the tablet produced by the latter and that the configuration of tablets suggested by the former cannot be used to duplicate the release profiles of the latter.

10. A batch of 6000 triple layer tablets was manufactured according to the procedure described in Patent Application 10/697,473. Each tablet contained 50 mg of diclofenac, an antiarthritic drug, in first and in third layer, and 40 mg of omeprazole, a gastrointestinal motility agent, in second layer. The granulation compositions for diclofenac, omeprazole and structural coat are shown in Table 1, Table 2 and Table 3, *infra*, respectively. All of the excipients used are from the list presented in the 10/697,473 Application.

Table 1

Composition of First and Third Layer

Ingredients	Quantity	
	Per Tablet	Per 6000 Tablets
Diclofenac Sodium, BP/EP	100mg	600G
Hydroxypropylcellulose (Klucel EXF), USP	40mg	240G
Lactose (Pharmatose DCL 11), USP	58mg	348G
Purified water		
Sodium Stearyl Fumarate (PRUV), NF	2mg	12G

*evaporates on drying of granulation

Table 2

Composition of Second Layer

Ingredients	Quantity	
	Per Tablet	Per 6000 Tablets
Oméprazole Magnesium **	41.29 mg	247.74G
Hydroxypropylcellulose (Klucel EXF), USP	20.44 mg	122.64G
Lactose (Pharmatose DCL 11), USP	64.75 mg	388.50G
Purified water*		
Sodium Stearyl Fumarate (PRUV), NF	1.32 mg	7.92G

*evaporates on drying of granulation
** equivalent to 40 mg omeprazole

Table 3

Composition of Coat

Ingredients	Quantity	
	Per Tablet	Per 6000 Tablets
Ethylcellulose (EC-N7), USP	103mg	618G
Lactose (Pharmatose DCL 11), USP	90mg	540G
Kollidon SR, EP	103mg	618G
Sodium Stearyl Fumarate (PRUV), NF	3mg	18G

11. ***Diclofenac Granulation for first and third layer***

The composition of diclofenac granulation is shown in Table 1, *supra*. Diclofenac (sodium salt), Hydroxypropyl cellulose and lactose were blended in an appropriate size high shear blender and granulated with water. Granules were dried in a fluid bed drier to humidity content of less than 4%. The granules were sized through a 20 mesh screen. Sized granules were lubricated with sodium stearyl fumerate.

12. ***Omeprazole Granulation for second layer***

The composition of omeprazole is presented in Table 2, *supra*. Omeprazole, lactose and hydroxylpropyl cellulose were blended in an appropriate size high shear blender and granulated with water. Granules were dried in a fluid bed drier to humidity content of less than 3%. The granules were sized through a 20 mesh screen and were lubricated with sodium stearyl fumerate.

13. ***Coat Granulation***

The composition of coat granulation is presented in Table 3, *supra*. Ethyl cellulose, lactose, Kollidon SR were blended in a V-blender and then lubricated with sodium stearyl fumerate.

14. ***Compression of Triple layer cores***

Flat circular triple layer tablets were compressed on a compression machine fitted with 8.2mm punches. Granulation for each layer was fed, in order, to the die cavity and precompressed. First and third layers, each consisted of 100 mg of the diclofenac granulation and the second layer consisted of 132mg of the omeprazole granulation. Final compression force was set to produce 6.7mm to 7.1mm thick triple layer tablets having hardness in the range of 20 to 40 N. The average weight of core was 332mg.

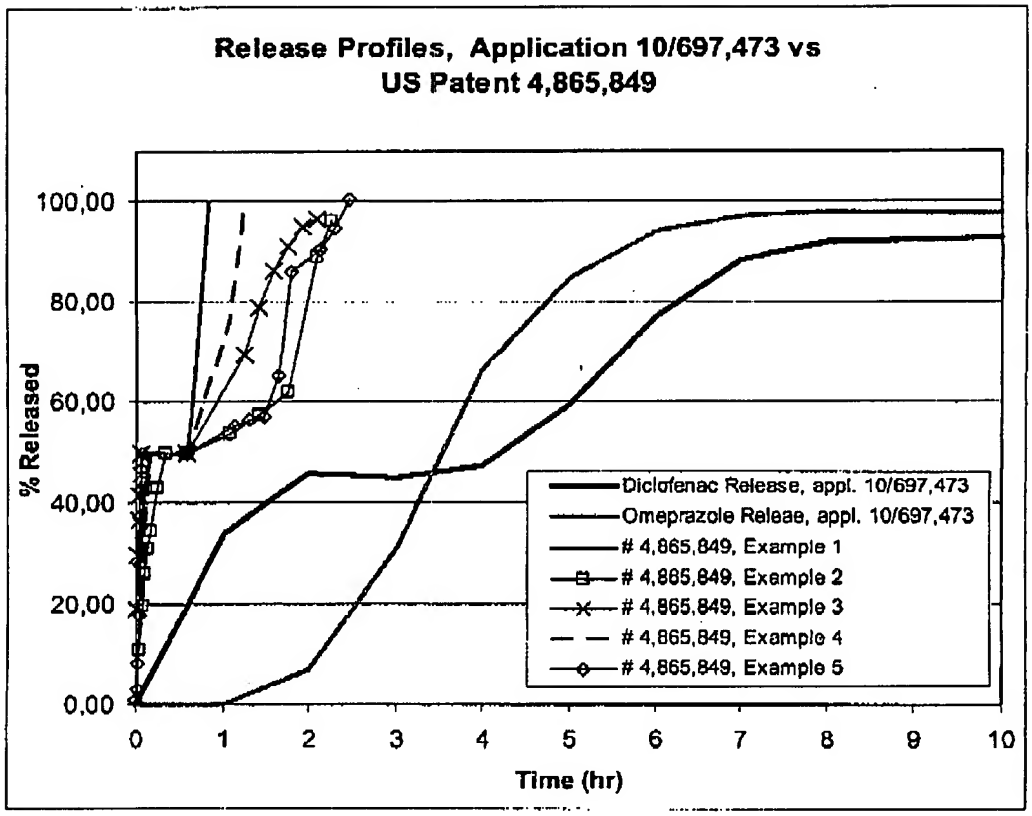
15. ***Compression Coating of Cores***

The prepared triple layer cores were compression coated on a machine using 11.2mm circular flat punches. For each core, 300 mg of coat formulation was transfered to the die cavity followed by placement of the core on the coat granulation bed. Compression force was set to produce coated triple layer tablets of hardness greater than 200 N, and thickness in the range 6.0mm to 6.6mm. Upper face of the core remains uncoated. The average weight of the triple layer coated tablet was 662mg.

16. ***In Vitro* Results**

The dissolution profile of the triple layer tablets was determined in pH10 borate buffer dissolution medium using the USP paddle method with the paddle rotation speed set at 100rpm, at a temperature of 37°C. The tablets were placed at the bottom of the vessel directly underneath the paddle. Samples of the dissolution medium were taken at regular intervals and assayed for concentration of the two drugs by HPLC. The release profiles of the two drugs from the above tablets are shown in **Figure 1, *infra***. For comparison purposes, plots using the data from the five examples provided in US Patent 4,865,849 are also presented in Figure 1. From the figure, it is readily apparent that the drug release time spans of the tablets in Conte US patent 4,865,849 and those from Patent Application 10/697,473 are vastly different. The release of drug from the first layer of the Conte tablets occurs instantaneously and the drug from third layer is released with in minutes. The delay between the release from the two drug layers is approximately half an hour. The total drug release time is approximately two hours. In contrast, it takes approximately eight hours for the two drugs to be released from the tablets prepared as per Patent Application 10/697,483. The release of drugs from the three layers is linear. The delay of release between the first and the third layer is approximately two hours. The second layer containing the drug omeprazole also acts as a barrier between the first and the second layer.

Figure 1



17. I further confirm and attest to the fact that the comparison of data presented in this study confirms that the configuration presented in Patent application 10/697,473 is different from that presented in US Patent 4,865,849. The linear release that occurs from the Patent Application 10/697,483 tablets is due to the constant surface area of the release face and maintenance of the shape and surface area throughout the dissolution process. Chronotherapy tablets within the scope of the 10/697,473 claims are cylindrical and comprise a coating which envelops the core *and* exhibit at least one exposed release face substantially perpendicular to the longitudinal axis of the core (i.e., the area of a disc).

18. The long time span achieved by these tablets will be useful in chronotherapy of arthritic patients. A tablet given at bed time will provide relief from early morning severe pain

experienced by the sufferers of arthritis. In contrast, a short span of drug release from tablets prepared according to Patent 4,866,849 cannot be used for chronotherapy. The short span of release from these tablets occurs because of the composition and protrusion of the first layer of the core from the coating shell. The protrusion promotes rapid dissolution . Even if same formulation was used by the two configurations, the release profile will still be vastly different due to difference in shape.

10. I further confirm and attest to the fact that evidence presented in this declaration illustrate that drug release profiles achieved by tablets defined by the claims of the United States Application Serial No. 10/697,473 cannot be achieved by tablets disclosed and contemplated by Conte in U.S. Patent 4,865,849.

Respectfully submitted,

By: _____

Dr. Alain Desjardins

Date: Oct. 29/2007

APPENDIX

CURRICULUM VITAE

Dr. Alain Desjardins

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WORK EXPERIENCE

2004- Now
Director ('04, '05), V.-P. ('06) R&D, Mistral Pharma Inc.

Main Responsibilities:

- Supervise the development and act as technical contact person for projects development performed by collaborators or outsourced.
- Set-up a R&D formulation laboratory by hiring personal and purchasing formulation equipments.
- Initiate work on new projects oriented toward development of Mistral's most advanced technologies, or new products. Lead the development of prototypes of new products. Select most promising formulation, prepare stability batches, and obtain supporting stability data. Proceed with scale-ups, pilot batches, and clinical batches. Plan and outsource clinical studies Assist transfer to production facilities, and collaborate to validation protocol approval. Find and make available to third party manufacturer the specialized equipment required to manufacture products based on Mistral's technologies.
- Plan and supervise the work of the product development team to meet corporation's targets and milestones. Establish and respect the budget. Anticipate equipment needs and obtain approval for purchasing. Maintain and improve premises. Ensure team is working efficiently by providing necessary working tools, clear directions, and a positive psychological environment.
- Generate intellectual property and provide technical basis for patent application.
- Assist Upper Management and Business Development by providing technical and scientific assessments on new products/ projects.

2001- 2004
Manager, Pharmaceutical Development, Church & Dwight Canada (Formerly Carter-Horner Inc)

Main Responsibilities:

- Plan and supervise the work of the product development team to meet corporation's targets and milestones. Establish and respect the budget. Anticipate equipment needs and obtain approval for purchasing. Maintain and improve premises.
- Develop prototypes of new products or line extensions. Select most promising formulation, prepare stability batches, and obtain supporting stability data. Proceed with scale-ups and pilot batches. Assist transfer to production facilities, and collaborate to validation protocol approval. Dosage forms: solid, cream, and liquids.
- Assist Business Development initiatives by providing technical and scientific assessments on: new products, new product sources, licensing opportunities and technologies. Suggest new products, new concepts, and identify new technologies and delivery systems.
- Report progress on product development on a monthly basis to the New Product Steering Committee, which also includes representatives from Business Development, Marketing, and Regulatory departments.

- Technical support to Manufacturing and to existing products:
  - •Trouble shooting existing products
  - •Optimize existing products and/or processes
  - •Develop new processes for existing products

  - •Improve product stability to increase shelf-life•Evaluate alternate ingredients or suppliers
  - •Evaluate changes in processing or formulation
  - •Emits new manufacturing batch records and approve changes on current ones

Main achievements:

- 2002:
  - Gravol Long Acting Caplet, DIN 02244808, launched Sept 02
  - Gravol Ginger Natural Source, DIN 02245718, launched Sept. 02
  - Gravol Gelcap, DIN 02245867, launched Sept. 02
  - Arm & Hammer Roll-on, production transferred from US to Mtl site, Nov. 02

Main achievements (cont'd):

- 2003/04:
  - Reformulation of:
    - Ovol 160 mg to 180 mg, DIN 02247127, Q2/03; Diovol suspension (antacid), to be launched Q1/04; Fermentol (disgestive aid), to be launched

Q1/04; Carter's Little Pill (bisacodyl 5mg, previously US produced), to be launched Q2/04

- Rub A535 Ancient Secret, DIN 02248564, launched Feb 04 ;
- Rub A535 Dual Action, DIN 02248563, launched Feb 04
- Gravol Dual Action Bilayer, launch planned for Q4/04
- Gravol Ginger Lozenge, DIN 02248180, launch planned for Q2/04
- Gravol Mouth Dissolving tablet, launch planned for Q3/04

1997-2000
Manager, formulation group, Labopharm Inc.

Responsibilities:

- Plan and supervise the work of the formulation team. Optimize the operation of the production units and of the dissolution laboratory.
- Review the progress of the various projects on a daily basis. Ensure that experiments are well documented, and review laboratory notebooks regularly. Write progress reports.
- Contribute actively to the resolution of problems and to the generation of new ideas in formulation. Contribute to new patent generation. Advise the director of R&D on research orientation.
- Perform scaling-up of new formulations from laboratory to pre-industrial level. Plan and supervise the production of clinical lots.
- Promote the respect of SOPs, of standard methods, of GMPs, and of GLPs.

Main achievements:

- Development of over 20 controlled-release formulations.
- Scaling-up of these formulations at the pre-industrial level.
- Planning and supervision of the production of 15 clinical lots.
- Development of several wet granulation and film coating protocols. Training of formulators on various equipments such as rotary presses, drycoating press, film coater, fluid bed and high shear granulators.
- One patent submitted on a new control-release technology.

1992 - 1997
Project leader, Johnson & Johnson, Research and Development

Responsibilities:

- Act as the main source of information on chemical matters for the research centre.
- Develop analytical, physico-chemical, and physical test methods.
- Solve chemical and physico-chemical problems to optimise the production of an absorbent board based on sphagnum.

- Develop new absorbent materials based on sphagnum or improve existing products, as well as perform the technological transfer from pilot to commercial level.
- Initiate, conduct or supervise fundamental or applied studies on sphagnum and sphagnum based products. Write technical reports and communicate them.
- Offer analytical and technical support to marketing.

Main achievements:

- Development of analytical methods to quantify process chemical additives (surfactants). These methods were used for the concentration mapping of additives in various points of the process.
- Cost reduction by the optimization of the use of process chemical aids.
- Plant effluent made non-toxic without any investment or increase in operating cost.
- Development of analytical methods (GC) to quantify urinary and menstrual odours.
- Development of an absorbent that controls urinary and menstrual odours.
- Development of a germination mat based on sphagnum. Patent.

1991-92
Post-doctoral fellow, Pulp and Paper Institute of Canada (PAPRICAN)
Subject: Modification of paper properties by latex incorporation.

Summer 1986
(a) McGill University

Subject: Synthesis of biopolymers and study of their billirubin adsorption capacity.

Summer 1985
McGill University
Subject: Synthesis and study of some reactions of organometallic compounds of titanium.

EDUCATION

1986-91

Doctor of Philosophy – Chemistry (physical and polymer chemistry)
McGill University, Montréal

Subject: Synthesis and study of the colloidal and mechanical properties of styrene/methacrylate based block ionomers.

1983-86

Bachelor of Science - Honors in Chemistry
McGill University, Montréal

SCHOLARSHIPS AND AWARDS

Graduate scholarships:

Fonds pour la formation de chercheurs et l'aide à la recherche (F.C.A.R.), 1990-91.

Natural Sciences and Engineering Research Council of Canada (N.S.E.R.C.), 1986-90.

Undergraduate awards:

1985-6:	University Scholar First class Honors Society of Chemical Industry Merit Award Anne Molson Prize BASF Canada Inc. Award Anachemia Prize in Chemistry N.S.E.R.C. summer research scholarship
1984-5	John Wakley Award Chemical Institute Medal and Prize
1983-4	Faculty Scholar

PUBLICATIONS

1. A. Shaver, S. Morris, A. Desjardins, The Reaction of (C5H5)2Ti(SR)2 with Benzyl Bromide and Bromine to Give Sulfides and Disulfides, Respectively. *Inorganic Chimica Acta, 1989, 161, 11-12.*

2. A. Desjardins, The Colloïdal and Dynamic Mechanical Properties of Styrene/Methacrylate Based Block Ionomers. *Doctoral thesis, McGill University, 1991.*

3. A. Desjardins, A. Eisenberg, Colloïdal Properties of Block Ionomers. 1. Characterization of Reverse Micelles of Styrene-b-Metal Methacrylate Diblocks by Size-Exclusion Chromatography. *Macromolecules, 1991, 24, 5779-5790.*

4- A. Desjardins, T.G.M. van de Ven, A. Eisenberg, Colloïdal Properties of Block Ionomers. 2. Characterization of Reverse Micelles of Styrene-b-Methacrylic Acid and Styrene-b-Metal Methacrylate Diblocks by Dynamic Light Scattering. *Macromolecules, 1992, 25, 2412-2421.*

5- A. Desjardins, A. Eisenberg, Dynamic Mechanical Properties of Triblock Ionomers of Polystyrene and Poly(sodium methacrylate). *Plastics Rubber and Composites: Processing and Applications, 1992, 18, 161-168.*

6- L. Gao, A. Desjardins, A. Eisenberg, Solubilisation Equilibria of Water in Nonaqueous Solutions of Block Ionomers Reverse Micelles: An NMR Study. *Macromolecules, 1992, 25, 1300-3.*

7- *K. Yoshikawa, A. Desjardins, J. M. Dealy, A Eisenberg, The Rheological Properties of Polystyrene-b-poly(sodium methacrylate) Diblock Ionomers. Submitted to Macromolecules..*

8- N. Pelletier, A. Desjardins, L Lageux, Plant Seed Germination Mat, Canadian Patent # 2,207,227, International Patent # WO 98/56232 (assigned to Johnson & Johnson). International application number PCT/CA98/00561

9- J. Bacon, A. Desjardins, M. Rahmouni, V. Lenaerts, Prolamine Based Sustained-Release Composition and Delayed-Onset Compositions, (assigned to Labopharm). International patent application WO 0243706, also US 202106408, CA 2433668.

10- A. Desjardins, B. Bolduc, Controlled-Release Oral Dosage Form, (assigned to Mistral Pharma), US provisional application 60/722971.

CONFERENCE & POSTER PRESENTATIONS

1- Colloïdal Properties of Block Ionomers.
A. Desjardins, J.-P. Gouin, T.G.M. van de Ven, C.E. Williams, A. Eisenberg
IUPAC 33e International Symposium on Macromolecules, Montréal (1990).

2- Les propriétés colloïdales de copolymères séquencés partiellement ioniques.
A. Desjardins, J.-P. Gouin, T.G.M. van de Ven, C.E. Williams, A. Eisenberg
58e congrès de l'ACFAS, Québec (1990).

3- In-vivo Evaluation of Controlled-Release Tablet Formulation of Levalbuterol Hydrochloride.
A Desjardins and al., presented at the *American Association of Pharmaceutical Scientist,*

New Orleans, USA, 1999.

4- Development and Scale-up of Compression-coated Levalbuterol Controlled Released Tablets Using Contramid Technology.
A. Desjardins , M. Bouzerda, F. Chouinard, *Proceed. Int'l Symp. Control. Rel. Bioact.*

Mater.,, 26 (1999), Controlled Release Society, Paris, France.

OTHER INFORMATION

Language	French and English (oral and written)
Social implication	Vice-president, Coop des Moissons (1988-89) President, Coop des Moissons (1990) Secretary, Coop des Moissons (1991)